

Effects of blood pressure level management on maternal and perinatal outcomes in pregnant women with mild to moderate gestational hypertension

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ABSTRACT

Objectives: This study aims to investigate the effects of blood pressure control level on maternal and perinatal outcomes in pregnant women with mild to moderate gestational hypertension (GHp).

Material and methods: A total of 344 pregnant women who initially diagnosed as mild to moderate gestational hypertension were recruited in this study. They were divided into 4 groups according to the stabilized blood pressure level (BPL) during pregnancy. The clinical parameters and the incidence of adverse pregnancy outcomes were compared among the four groups. The association between blood pressure levels and relative factors were analyzed using the χ^2 test. Multivariate logistic regression analysis was adopted for risk factors associated with adverse pregnancy outcomes.

Results: The results showed the prevalence of obesity was significantly associated with blood pressure levels of mild-moderate GHp pregnant women ($p = 0.029$). The incidence of severe GHp, SPE in group A, group B, and group C were statistically significant ($p < 0.001$, $p = 0.041$, respectively). In the patients who used drugs to control BPL, the incidence of severe GHp has a significant association with the initial blood pressure levels ($p = 0.004$). However, no significant difference was found in the incidence of sPE, PE + Upro, and SGA (all $p > 0.05$). Multivariate logistic regression analyses results showed that the gestational factor BPL was an independent risk factor for the incidence of sGHp. The AMA, primigravida, gestational BPL, and edema were risk factors for the incidence of preeclampsia with proteinuria. To the incidence of sPE, gestational BPL is the independent risk factor. Finally, preeclampsia anamnesis and FGR trend are the high-risk parameters to the incidence of SGA.

Conclusions: Timely management and control of blood pressure in pregnant women with mild to moderate GHp were beneficial to reduce the occurrence of severe GHp and sPE, but the incidence of SGA does not affected.

Key words: blood pressure level; pregnancy; maternal outcome; perinatal outcome; preeclampsia; hypertension in pregnancy; adverse pregnant outcomes

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INTRODUCTION

Hypertensive disorder complicating pregnancy (HDCP) is a common complication of pregnancy, with a spectrum of conditions that include chronic hypertension, gestational hypertension (GHp), preeclampsia (PE), severe PE (sPE), eclampsia, and chronic hypertension with preeclampsia. HDCP is one of the main causes of maternal and perinatal morbidity and mortality, which seriously affects the health of mother and fetal [1, 2]. Pregnancy with hypertension affected 6–8% of pregnancies in the USA, and about 5.22% of pregnancies in China [3, 4]. In addition to maternal cerebrovascular and cardiac complications, HDCP is also associated with small for gestational age (SGA) infants and preterm birth [5–7].

Previous study by Buchbinder A et al. [6] showed the adverse perinatal outcomes were higher in women with severe gestational hypertension than in mild preeclampsia. A study by Mudjari NS et al. [8] pointed that the management of hypertension in pregnancy by preventing women from getting the risks of increased blood pressure (BP) can reduce maternal and perinatal morbidity and mortality.

The prevention, early diagnosis, and treatment of HDCP can reduce the risk of maternal and fetal complications [9–11]. In most regions of the world, severe gestational hypertension was diagnosed when the blood pressure during pregnancy is more than 160/110 mm Hg [12–14]. It has reached a consensus on the antihypertensive treatment

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of severe gestational hypertension, and it is necessary to control the blood pressure when the severe gestational hypertension occurs. However, there are still different views on when the treatment of hypertension should be initiated for pregnant women with mild-moderate gestational hypertension (systolic blood pressure 140–159 mm Hg and diastolic blood pressure 90–109 mm Hg). According to the report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy, it is suggested that anti-hypertensive medications not be administered for women with mild gestational hypertension or preeclampsia with a persistent blood pressure of less than 160/110 mm Hg [12]. Whereas some other countries, such as Canada, Australia, China, and so on, believe that the treatment of anti-hypertensive can also be considered in women with mild-moderate gestational hypertensive [13–15]. Therefore, to optimize the management of blood pressure in pregnancies with mild-moderate hypertensive is necessary for reducing maternal and perinatal morbidity and mortality.

Objectives

In the present study, we compared the clinical factors associated with GHp and incidence rates of severe GHp, preeclampsia with proteinuria (PE + Upro), sPE and SGA. This study aims to investigate the effects of blood pressure control level on perinatal outcomes in women with mild-moderate gestational hypertension.

MATERIAL AND METHODS

Study Population

A total of 344 pregnant women (aged from 21 to 44, the average age was 30.15 ± 5.15 years; gestational age of 20–32 weeks, the average gestational age was 25.75 ± 2.24 weeks) were included between January 2012 and December 2016 in The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, Zhejiang). Eligible women were those who have had regular antenatal examinations, carried the pregnancy to term, and initially diagnosed with mild to moderate gestational hypertensive. The women with multiple pregnancies, fetal chromosomal abnormalities, placenta previa, spontaneous abortion, or induced abortion before 20 weeks of pregnancy were excluded. The clinical information was collected in this study including maternal age, maternal pre-pregnancy BMI, recurrent spontaneous abortion (RSA), previous history of preeclampsia, and maternal syndrome (such as nephritis and kidney disease syndrome, thyroid disorder, glucose metabolism, immune system disease, and polycystic ovarian syndrome). Obesity is usually classified by BMI. According to the criteria recommended by Working Group on Obesity in China, BMI was grouped into three categories: normal weight ($< 24.0 \text{ kg/m}^2$), over-

weight (≥ 24.0 and $< 28 \text{ kg/m}^2$), and obesity ($\geq 28.0 \text{ kg/m}^2$). The detailed clinical characteristics were summarized in Table 1 and Table 2. The study protocol was approved by the Ethical Approval of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants signed informed consent.

Definition and classification

According to the stabilized blood pressure level (BPL) during pregnancy, the participants were divided into four groups, including A, B, C, and D group. Group A includes 135 pregnancy women (BPL $< 130/80$ mm Hg). Group B includes 160 participants with systolic blood pressure between 130 and 139 mm Hg, and diastolic blood pressure between 80 and 89 mm Hg. Group C obtained 46 participants with systolic blood pressure between 140 and 149 mm Hg, and diastolic blood pressure between 90 and 99 mm Hg. Group D includes 3 participants with systolic blood pressure between 150 and 159 mm Hg, and diastolic blood pressure between 100 and 109 mm Hg.

Diagnostic Criteria

The diagnosis of HDGP, including GHp, PE, and sPE, was based on the diagnosis and treatment guideline of hypertensive disorders during pregnancy [16]. Pregnancy complications, obtaining gestational diabetes mellitus (GDM), small for gestational age (SGA), fetal growth restriction (FGR), polycystic ovarian syndrome (PCOS), immune system disease, and other gestational complications, were also analyzed in the study. The diagnosis of GDM was based on the results of an oral glucose tolerance test [17]. Wessel's modified criteria were used to define the SGA infants. The predictive factors of PE mainly include prehypertension, excess body mass ($> 0.5 \text{ kg}$ per week), edema, hypoalbuminemia, decreased platelet level, and FGR trend. PCOS was defined according to the consensus on women's health aspects of PCOS [18].

Blood pressure control method

The management of blood pressure during pregnancy was controlled using oral drug therapeutic approach (labetalol or nifedipine) and lifestyle interventions. Lifestyle interventions, such as rest, diet control, adjustment of mental and environmental factors, are of proven benefit in gestational hypertensive. Among the participants in this study, there are 48 pregnancy women used therapeutic drug approach to control the blood pressure. What's more, the placental and fetal growth status were detected during the anti-hypertensive treatment.

Statistical analysis

Statistical analysis was carried out using SPSS software (SPSS, Inc., Chicago, IL, USA). Data are expressed as

Table 1. The relationship between blood pressure level and parameters of GHp women

Parameters	Cases (n = 344)	GHp women groups				p
		A (n = 135)	B (n = 160)	C (n = 46)	D (n = 3)	
Gestational age	25.75 ± 2.24	25.93 ± 2.18	25.46 ± 2.18	26.20 ± 2.71	26.33 ± 3.51	0.134
RSA						0.951
No	323	126	151	43	3	
Yes	21	9	9	3	0	
AMA						0.070
No	254	100	125	27	2	
Yes	90	35	35	19	1	
Obesity						0.029
No	301	124	140	35	2	
Yes	43	11	20	2	1	
PE anamnesis						0.182
No	335	134	155	43	3	
Yes	9	1	5	3	0	
Primigravida						0.056
No	169	62	75	29	3	
Yes	175	73	85	17	0	
Primiparity						0.524
No	29	8	16	5	0	
Yes	315	127	144	41	3	
Pregnancy complications						0.370
No	204	82	95	24	3	
Yes	140	53	65	22	0	

RSA — recurrent spontaneous abortion; AMA — advanced maternal age (pregnant women aged 35 years or over)

Table 2. Prevalence of adverse pregnancy outcomes in relation to blood pressure levels

Outcomes	Cases (n = 344)	GHp women groups				p
		A (n = 135)	B (n = 160)	C (n = 46)	D (n = 3)	
Severe GHp						< 0.001
No	322	134	149	36	3	
Yes	22	1	11	10	0	
PE + Upro						0.311
No	242	98	113	28	3	
Yes	102	37	47	18	0	
sPE						0.041
No	296	122	137	34	3	
Yes	48	13	23	12	0	
SGA						0.813
No	314	124	144	43	3	
Yes	30	11	16	3	0	

Severe GHp — severe gestational hypertension; PE + Upro — preeclampsia with proteinuria; sPE — severe preeclampsia; SGA — small for gestational age

mean ± SD. The clinical profile and incidence of severe GHp, preeclampsia with proteinuria (PE + Upro), sPE, SGA were compared among the four groups. The differences between

two groups were examined by paired student's t tests. Maternal and perinatal outcomes were compared using χ^2 test and multivariable logistic regression to control for potential

Table 3. Comparison of pregnancy blood pressure levels and prevalence of adverse pregnancy outcomes in 48 mild-moderate GHp women using anti-hypertensive drugs

Outcomes	Cases (n = 48)	Prenatal BPL (mm Hg)			p
		< 130/80	(130–139)/(80–89)	(140–149)/(90–99)	
Severe GHp					0.007
No	31	9	18	4	
Yes	17	1	7	9	
PE + Upro					0.168
No	24	7	13	4	
Yes	24	3	12	9	
sPE					0.042
No	28	8	16	4	
Yes	20	2	9	9	
SGA					0.709
No	39	9	20	10	
Yes	9	1	5	3	

risk factors. P value less than 0.05 was considered to be statistically significant.

RESULTS

Association between blood pressure level and clinical characteristics of pregnant women

In the present study, we compared the clinical characteristics of four groups of pregnant women with mild-moderate GHp. The prevalence of obesity among pregnant women in group A is 8.1% (11/135), 12.5% (20/160) in group B, 23.9% (11/46) in group C, and 33.3% (1/3) in group D, which increased following the rising of BPL. The results showed the prevalence of obesity was significantly associated with blood pressure levels of mild-moderate GHp pregnant women ($p = 0.029$, Tab. 1). However, no positive associations were found with other clinical characteristics, such as gestational age, RSA, advanced maternal age (AMA; pregnant women aged 35 years or over), PE anamnesis, primigravida, primiparity, pregnancy complications (all $p > 0.05$, Tab. 1).

Prevalence of adverse pregnancy outcomes in relation to blood pressure levels

We also analyzed the incidence of adverse pregnancy outcomes in four groups of pregnant women. In group D, there was no occurrence of adverse pregnancy outcome. The incidence of severe GHp in group A (0.7%, 1/135), group B (6.9%, 11/160), and group C (21.7%, 10/46) was statistically significant ($p < 0.001$, Tab. 2). The incidence of sPE was also found (a significant difference among group A, group B, and group C) ($p = 0.041$, Tab. 2). However, there was no significant difference of incidence of preeclampsia with proteinuria (PE + Upro) and SGA (all $p > 0.05$).

The occurrence of adverse pregnancy outcomes in pregnant women with mild-moderate GHp after anti-hypertensive

In the present study, 48 participants were given anti-hypertensive drugs to control blood pressure. Among the pregnant women who used anti-hypertensive drugs, 10 pregnant women had BPL less than 130/80 mm Hg, 25 participants had a BPL of (130–139)/(80–89) mm Hg, and 13 pregnant women had a BPL of (140–149)/(90–99) mm Hg. As shown in Table 3, the incidence rates of severe GHp and sPE in pregnant women with different pregnancy blood pressure levels were significantly different (all $p < 0.05$). Among different pregnancy blood pressure levels groups, there was no dramatical difference in the incidence of preeclampsia with proteinuria and SGA (all $p > 0.05$).

As shown in Table 4, with the increase of initial blood pressure levels, the incidence of severe GHp (3/23, 7/15, 7/10) is significantly increased, which has a significant difference ($p = 0.004$). However, no significant difference was found in the incidence of sPE, PE + Upro, and SGA (all $p > 0.05$).

Risk parameters related to the incidence of adverse pregnancy outcomes

To analyze the risk parameters correlated with adverse pregnancy outcomes, we used the logistic regression analysis. As shown in Table 5, the factors gestational BPL (OR = 2.958, 95% CI = 1.293–6.766, $p = 0.010$) is the high risk parameters that significantly related to the incidence of sGHp. The AMA (OR = 0.112, 95% CI = 0.047–0.265, $p < 0.001$), primigravida (OR = 0.129, 95% CI = 0.070–0.238, $p < 0.001$), gestational BPL (OR = 1.903, 95% CI = 1.224–2.959, $p = 0.004$), and edema (OR = 2.698, 95% CI = 1.360–5.351, $p = 0.005$)

Table 4. Comparison of initial blood pressure levels and prevalence of adverse pregnancy outcomes in 48 mild-moderate GHp women using anti-hypertensive drugs

Outcomes	Cases (n = 48)	Initial BPL (mm Hg)			p
		(140–149)/(90–99)	(150–159)/(100–109)	≥ 160/110	
Severe GHp					0.004
No	31	20	8	3	
Yes	17	3	7	7	
PE + Upro					0.651
No	24	13	7	4	
Yes	24	7	8	6	
sPE					0.392
No	28	14	10	4	
Yes	20	9	5	6	
SGA					0.805
No	39	18	13	8	
Yes	9	5	2	2	

Table 5. Logistic regression analysis of factors contributing to adverse pregnancy outcomes

Outcomes	Variables	p	OR	95% CI
sGHp	Gestational BPL	0.010	2.958	1.293–6.766
PE + Upro	AMA	< 0.001	0.112	0.047–0.265
	Primigravida	< 0.001	0.129	0.070–0.238
	Gestational BPL	0.004	1.903	1.224–2.959
	Edema	0.005	2.698	1.360–5.351
sPE	Gestational BPL	0.030	1.814	1.060–3.104
SGA	PE anamnesis	0.020	6.866	1.347–34.998
	FGR trend	0.004	3.993	1.565–10.189

FGR trend — uterine length and abdominal circumference were all below the 10th percentile for 3 consecutive weeks

are risk factors for the incidence of preeclampsia with proteinuria. To the incidence of sPE, gestational BPL (OR = 1.814, 95% CI = 1.060–3.104, $p = 0.030$) is the independent risk factor. Finally, preeclampsia anamnesis (OR = 6.866, 95% CI = 1.347–34.998, $p = 0.021$) and FGR trend (OR = 3.993, 95% CI = 1.565–10.189, $p = 0.004$) are the high risk parameters that dramatically associated with the incidence of SGA.

DISCUSSION

Gestational hypertensive is one of the common complications in pregnancy, which is initial occurred hypertension after 20 weeks of gestation and will return to normal within 12 weeks after delivery. Light GHp can be asymptomatic or mild dizziness, slightly elevated blood pressure, accompanied by edema or mild proteinuria, severe GHp may cause important organs injury, occur PE or eclampsia. PE and eclampsia are the main cause of adverse maternal and perinatal outcomes, such as intrauterine growth restriction and

preterm birth [19, 20]. The study by Schokker SA et al. [21] showed previous hypertensive disorders of pregnancy was an independent risk factor for later vascular morbidity. Therefore, controlling pregnancy blood pressure can avoid organ or placenta injury and reduce the occurrence of serious adverse maternal and perinatal outcomes.

Previous studies have shown that the treatment of severe GHp can minimize the fluctuation of blood pressure during pregnancy and reduce the future risk of vascular (such as cerebrovascular and/or cardiovascular disease) disease [21–25]. A study by Choi DJ et al. [22] showed that a family history of premature cardiovascular disease was significantly associated with gestational hypertensive disease. The study by Abalos E et al. [23] showed that with the use of antihypertensive drugs could reduce the risk of developing severe hypertension, but no clear differences in the risk of other developing outcomes were found. Molvi SN et al. [24] also found antihypertensive therapy was associated with a lower incidence of severe pregnancy-induced hypertension, proteinuria, SGA babies, as well as some other maternal and fetal-neonatal non-fatal adverse events. A previous study suggested that anti-hypertensive treatment when BPL > 140/90 mm Hg, coupled with close fetal monitoring, might result in both improved fetal outcome, as well as decreasing immediate maternal complications and permanent vascular injury [25]. However, whether anti-hypertensive drug therapy for women with mild or moderate GHp is still controversial.

In the present study, we analyzed the clinical parameters of pregnant women with mild to moderate GHp. We found the prevalence of obesity was significantly associated with blood pressure levels of mild-moderate GHp pregnant women. Some studies have indicated obesity was associated

with blood pressure and increased risks of GHP. For instance, Gaillard R et al. [26] suggested maternal obesity and morbid obesity were strongly associated with the risk of gestational hypertensive disorders. Pregnancy is a period of substantial change in blood pressure, with physiological blood pressure decreasing before the middle stage of pregnancy, and then increasing until delivery [27–29]. In this study, we also analyzed the incidence of adverse pregnancy outcomes in pregnant women with different BPL. The results showed that the incidence of severe GHP in group A (0.7%, 1/135), group B (6.9%, 11/160), and group C (21.7%, 10/46) was statistically significant, which showed an increasing trend with the BPL level. The incidence of sPE was consistent with that of severe GHP. But in group D, there was no occurrence of adverse pregnancy outcome, which might be related to only 3 cases, as the small sample size was prone to bias. Then we further investigated the adverse pregnancy outcomes in pregnant women who took BPL medications. Among 48 pregnant women who used anti-hypertensive drugs, 10 pregnant women had BPL less than 130/80 mm Hg, 25 participants had a BPL of (130–139)/(80–89) mm Hg, and 13 pregnant women had a BPL of (140–149)/(90–99) mm Hg. After anti-hypertensive treatment, the incidence rates of severe GHP and severe eclampsia in pregnant women with different pregnancy blood pressure levels were also found significantly different. However, there was no dramatical difference in the incidence of preeclampsia with proteinuria and SGA. The occurrence and development of mild to moderate GHP may be influenced by multiple factors. Multivariate logistic regression analysis results showed gestational BPL was an independent risk factor for the incidence of severe GHP and sPE. Hence, low blood pressure during pregnancy in GHP women can help reduce the occurrence of severe GHP and sPE, and will not lead to increased incidence of SGA.

What's more, we analyzed initial blood pressure levels and prevalence of adverse pregnancy outcomes in mild-moderate GHP women using anti-hypertensive drugs. The results showed that the incidence of preeclampsia with proteinuria, sPE, and SGA have no significant difference with the initial BPL in mild to moderate pregnant women who had anti-hypertensive treatment, and only the difference in the incidence of severe GHP was statistically significant. The results indicated with the increase of initial blood pressure levels, the incidence of severe GHP (3/23, 7/15, 7/10) was significantly increased. According to the multivariate logistic regression analysis results, the initial BPL was an independent risk factor for the incidence of severe GHP, which suggested timely management and control of blood pressure in pregnant women with mild to moderate GHP was beneficial to reduce the occurrence of severe GHP.

The multivariate logistic regression analysis results also showed edema was risk factor that significantly associated

with preeclampsia with proteinuria. The pregnant women with edema show a higher incidence of preeclampsia with proteinuria than those without edema. Therefore, it is necessary to observe the occurrence of edema for preventing the incidence of PE. According to the results of detection of placental and fetal growth status during the anti-hypertensive treatment, there was no affection to the incidence of SGA. Multivariate logistic regression analysis results show the factors gestational BPL is the high-risk parameters that significantly related to the incidence of sGHP. The AMA, primigravida, gestational BPL, and edema are risk factors for the incidence of preeclampsia with proteinuria. To the incidence of sPE, gestational BPL is an independent risk factor. Finally, preeclampsia anamnesis and FGR trend are the high-risk parameters that dramatically associated with the incidence of SGA. These results showed that the risk factors influencing the incidence of adverse pregnancy outcomes were very complicated. The gestational BPL was found significantly associated with the incidence of severe GHP, preeclampsia with proteinuria, and sPE. To control the gestational BPL is beneficial to delay the progression of severe GHP, and reduce the incidence of sPE.

In considering the results of this study, some limitations need to be addressed. First, the sample size of patients is limited. A large number of subjects can improve the accuracy of the results. Second, part of the clinical data was not completed, and more parameters can be involved in the further analyses. Due to the limitations, further analyses are necessary for large research cohort and more parameters.

CONCLUSIONS

In conclusion, timely management and control of blood pressure in pregnant women with mild to moderate GHP was beneficial to delay the progression of severe GHP, and reduce the occurrence of sPE. What's more, there is no correlation was found with the incidence of SGA. Meanwhile, due to the regular prenatal examination and the diversification of diagnostic methods, mild to moderate GHP pregnant women can be timely diagnosed.

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